Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1591510
J Health Sci Med. 2025;8(2):292-297

Does the presence of comorbidities in rheumatoid arthritis patients impact initial tumor necrosis factor inhibitor treatment response and retention rates?

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Cite this article as: Yüce İnel T, Kocaer SB, Dalkılıç HE, et al. Does the presence of comorbidities in rheumatoid arthritis patients impact initial tumor necrosis factor inhibitor treatment response and retention rates? *J Health Sci Med.* 2025;8(2):292-297.

Received: 02.12.2024 ◆ **Accepted**: 17.02.2025 ◆ **Published**: 21.03.2025

ABSTRACT

Aims: We aimed to evaluate the effect of comorbidities on the first tumor necrosis factor inhibitor (TNFi) treatment response and retention in patients with rheumatoid arthritis (RA).

Methods: The study included adult RA patients (with M05 and M06 ICD codes) registered in the TURKBIO database and receiving their first TNFi treatment. Data on demographic, clinical, and laboratory features, disease activity scores, and other follow-up parameters (at the beginning and months 6 and 12) were collected. The Log-Rank test and Kaplan-Meier curve were used to determine the TNFi retention rates.

Results: There were 1172 bio-naive RA patients who initiated their first TNFi treatments. The median age (IQR) of the patients was 53 (51-61), and 79.8% (n=935) were women. The most commonly used TNFi was etanercept (38.9%), followed by adalimumab (27.9%), certolizumab (13.8%), golimumab (10.8%), and infliximab (8.7%). The most prevalent comorbidities in patients were hypertension (32.6%), obesity (32.6%), osteoporosis (22.3%), asthma/COPD (17.9%), and diabetes mellitus (15.7%). The presence of comorbidities at the beginning of TNFi treatment did not affect DAS28 CRP responses at months 6 and 12 (p=0.18 and p=0.83, respectively) and the continuation rates of the first TNFi drug. After conducting a thorough analysis that factored in variables including gender, age over 60 years, smoking, serologic status, presence of erosion, and basal disease activity scores, it was determined that there were no statistically significant hazard ratios (HR) for the first TNFi persistence. However, there was a 5% decrease in adherence to the first TNFi drug with an increase in median disease duration (HR 0.95, 95% CI=0.90-1.00, p=0.048).

Conclusion: It has been observed that the presence of comorbidities in patients with RA does not significantly affect the TNFi treatment response and retention rate. However, evidence suggests that as the duration of the disease increases, the continuation of the first TNFi drug may decrease.

Keywords: Comorbidity, rheumatoid arthritis, first TNFi drug survival

*The article was presented as a poster at the EULAR 2020 congress in Madrid.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder primarily affecting the joints, leading to synovium inflammation and cartilage damage.[1] The prognosis for individuals with RA has significantly improved with the use of biological agents and close patient monitoring to succeed in low disease activity or remission. However, the presence

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of comorbidities can lead to functional limitations[2] and premature mortality in patients with RA.[3] Comorbidities may manifest in RA patients as a consequence of treatments or as a direct association with RA itself. Of the 5,317 patients, 18.3% displayed at least one comorbidity, according to the Charlson Comorbidity Index (CCI).[4] In RA, the prevalence of multimorbidity is remarkably high and is associated with a faster progression compared to individuals without RA.[5] The presence of comorbid conditions presents challenges in the management of RA, such as contraindications for medications or patient noncompliance with treatment.[6] Additionally, there is growing recognition of the significant impact that comorbidities have on the development of difficult-to-treat RA.[7]

Tumor necrosis factor inhibitors are frequently prescribed biologic agents for the treatment of RA patients who have not shown improvement with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). But, approximately 30-40% of patients treated with tumor necrosis factor inhibitor (TNFi) cannot be continued due to primary/secondary ineffectiveness or side effects.[8-10] However, the patient population in clinical trials may differ from real-life patients regarding associated comorbid conditions and additional medications, potentially leading to differences in drug survival outcomes. With this study, we aimed to assess the impact of comorbidities on the persistence of the first TNFi in patients with RA and present real-life data.

METHODS

Ethics

Ethical approval for the use of TURKBIO data was granted under protocol number 304-SBKAEK, with all participating patients having provided written informed consent. The study was carried out with the permission of the Dokuz Eylül University Faculty of Medicine Ethics Committee (Date: 07.06.2013, Decision No: 107354). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Population

The study focuses on a patient population obtained from the TURKBIO registry, a multicenter observational cohort in Turkiye dedicated to patients receiving biologic treatments for rheumatic diseases. The TURKBIO database is the Turkish version of the Danish DANBIO rheumatology database established in 2011. Patient data are entered into an online system by physicians at three-month intervals or in response to any changes in medication. In Turkiye, the administration of TNFi treatments for RA is restricted to patients with a 28-joint count disease activity score (DAS28) exceeding 5.1, who have not responded adequately to at least three standard disease-modifying antirheumatic drugs (DMARDs), one of which must be methotrexate (MTX).

The inclusion criteria for this analysis comprised adult patients diagnosed with RA, identified through specific diagnostic codes (M05 and M06 ICD), who were beginning their first course of treatment with TNFi. The study targeted biologic-naive RA patients satisfying the 2010 ACR/EULAR classification criteria,[11] thereby ensuring a well-defined cohort for evaluation.

Data Collection

The study thoroughly evaluated demographic and clinical characteristics encompassing age, gender, disease duration, smoking status, body-mass index (BMI), and acute phase reactants, notably C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Serologic status indicators, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP), as well as disease activity scores (such as the Clinical Disease Activity Index, DAS28, and the Visual Analogue Scale Global), were meticulously assessed. Furthermore, the Health Assessment Questionnaire-Disability Index, X-Ray evidence of erosion, and various comorbidities were documented.

Comorbidities under examination included hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, cerebrovascular disease, obesity, osteoporosis, depression, chronic lung disease, liver disease, peripheral vascular disease, peptic ulcer disease, and renal disease. Additionally, patients with at least two comorbidities were defined as multi-comorbidities. The presence or absence of concomitant csDMARD and corticosteroid use was systematically recorded. However, dose calculation for these medications was not undertaken in this study. The exclusion criteria specified for the study were (i) patients lacking follow-up data and (ii) those who withdrew their informed consent.

The study assessed the persistence of the first TNFi treatment by calculating the duration between the first and last prescriptions. Drug retention was analyzed using Kaplan-Meier methods and a log-rank test to compare survival distributions. During anti-TNF therapy, disease activity was measured at baseline, 6 months, and 12 months. The data point closest to each time point was selected for analysis in cases with multiple visits within the specified intervals. Clinical responses were assessed using the DAS28 scale. A change in the DAS28 score greater than 1.2 is considered a significant improvement.

Statistical Analysis

Demographics and descriptive data are presented as median [interquartile range (IQR)] or mean (SD). The variables were checked for normal distribution using visual and analytical methods. Chi-square analysis was used for categorical variables, and the Mann-Whitney U test was used for pairwise group comparisons with non-normally distributed numerical variables. The adherence rates for the first TNFi were calculated using the Kaplan-Meier method. Risk factors associated with firstTNFi discontinuation were determined using Cox Regression analysis. Statistically significant results were considered at type-1 error levels below 5%.

RESULTS

The median age (IQR) of the RA patients was 53 (51-61) years, and 79.8% (n=935) were women. 23.2% (n=256) of the patients were smokers. RF was positive in 55.6% (n=404), and anti-CCP antibody was positive in 58.2% (n=430). At least one erosion on the radiographs was found in 61.9% of the patients (n=317). In the studied cohort, 44.2% of patients used concomitant csDMARDs, and 40.3% were prescribed

corticosteroids. The distribution of biologic therapies was as follows: etanercept was prescribed to 38.9% (n=456) of the patients, adalimumab to 27.9% (n=326), certolizumab to 13.8% (n=162), golimumab to 10.8% (n=126), and infliximab to 8.7% (n=102). The most commonly occurring coexisting disease included hypertension, which was present in 32.6% (n=262) of the patients, osteoporosis in 22.3% (n=178), asthma or chronic obstructive pulmonary disease in 17.9% (n=143), and diabetes mellitus in 15.7% (n=126). Around one-third of the patients exhibited a body-mass index of 30 or higher. The median CRP value among patients was 7 mg/L (3-18), while the median ESR was 26 mm/h (14-44). The study revealed that 66.3% (n=197) of seropositive RA patients exhibited at least one erosion on their radiographs, marking a statistically significant increase compared to seronegative patients (p=0.001). The demographic and clinical attributes of the bio-naive RA patients have been briefly outlined in Table 1.

Table 1. Demographic and clinical characteristics of patients

	n (%)
Gender (female)	935 (79.8)
Age*	53 (51-61)
Smoker	256 (23.2)
Rheumatoid factor positivity	404 (55.6)
Anti-cyclic citrullinated peptide positivity	430 (58.2)
Presence of erosion	317 (61.9)
Disease activity score 28 CRP*	3.9 (2.5-5.1)
CRP (mg/L)*	7 (3-18)
Erythrocyte sedimentation rate (mm/h)*	26 (14-44)
Visual Analogue Scale Global *	50 (20-70)
Health Assessment Questionnaire-Disability Index*	0.88 (0.38-1.25)
Comorbidities	
Hypertension	262 (32.6)
BMI ≥30	254 (32.6)
Osteoporosis	178 (22.3)
Pulmonary disease	143 (17.9)
Depression	126 (15.8)
Diabetes mellitus	126 (15.7)
Dyslipidemia	69 (8.7)
Kidney disease	47 (5.9)
Coronary artery disease	46 (5.7)
GERD/peptic ulcer	44 (5.5)
Hepatic disease	38 (4.7)
Peripheric vascular disease	16 (2)
Cerebrovascular disease	14 (1.7)

*Median, IQR: Interquartile range, CRP: C-reactive protein, BMI: Body-mass index, GERD: Gastroesophageal reflux disease

The first TNFi was initiated 9.2 (5.0-14.6) years after diagnosis in seropositive patients and 7.3 (2.8-11.5) years in seronegative patients (p=0.001). The median adherence rate of RA patients with at least one comorbid disease started on infliximab as the first bDMARD was 117.6 (±37.4) months. The presence of comorbidity did not affect the drug retention rate in RA patients using infliximab as their first TNFi (p=0.065). There was no statistically significant variance observed between the drug survival rates of etanercept users with or without comorbidities. (71.2 months and 87.3 months, respectively, p=0.56). No correlation existed between comorbidities and TNFi persistence in those using golimumab (p=0.66). The drug survival rate in patients initiated on certolizumab for RA was not found to be affected by the presence or absence of comorbidities (p=0.055). Similarly, there is no statistically significant variance between comorbidities and drug persistence when treated with adalimumab (p=0.94). Concomitant use of csDMARDs and/or steroids had no significant effect on the duration of the first TNFi (p=0.064, p=0.30, respectively).

The influence of hypertension, diabetes mellitus, coronary artery disease, or cerebrovascular disease on the adherence to the initial TNFi drug was insignificant (p=0.570, p=0.143, p=0.213, p=0.907, respectively). Similarly, dyslipidemia, peripheral vascular disease, pulmonary disease, or depression did not affect the first TNFi survival (p=0.140, p=0.631, p=0.199, and p=0.996). Notably, chronic kidney damage showed a marginally significant effect on drug persistence (p=0.051). At the same time, a body-mass index ≥30 did not affect the first TNFi drug survival (p=0.471). Having multi-comorbidity also did not affect retention on the first TNFi drug (p=0.829). Moreover, the presence of comorbidities at the beginning of TNFi treatment demonstrated no impact on DAS28 CRP responses at months 6 and 12 (p=0.18 and p=0.83, respectively). Overall, in rheumatoid arthritis, it was observed that comorbidities did not impact retention rates to the first TNFi drug (as illustrated in Figure) or the treatment response.

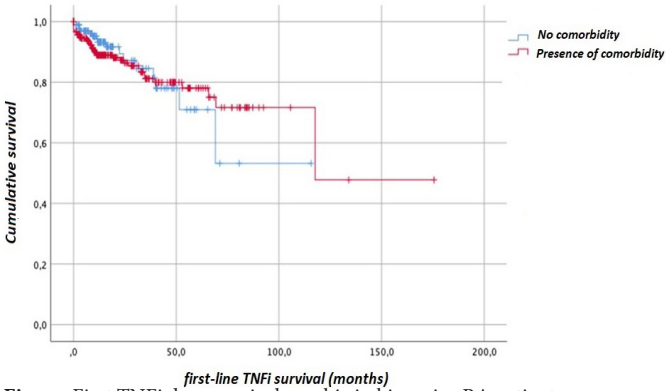

Figure. First TNFi drug survival graphic in bio-naive RA patients

TNFi: Tumor necrosis factor inhibitor, RA: Rheumatoid arthritis

Using variables including gender, age >60 years, smoking, seropositivity status, presence of erosion on X-Rays, and basal disease activity scores, no significant hazard ratios were obtained in the Cox proportional hazard analysis for the first TNFi persistence. In contrast, with the increase in median disease duration, adherence to the first TNFi decreases by 5% (HR 0.95, 95% CI: 0.90-1.00, p=0.048) (Table 2).

Table 2. Cox proportional hazard analysis for discontinuation of the first TNF inhibitor

Variable	HR	95% CI		p
Gender (male)	1.55	0.68	3.50	0.294
Age ≥60 years	0.72	0.31	1.67	0.446
Median disease duration (years)	0.94	0.89	1.00	0.052
Smoker	2.18	0.78	6.11	0.137
RF positivity	1.55	0.69	3.49	0.293
Presence of erosion	1.45	0.65	3.24	0.362
Basal HAQ	1.15	0.66	2.02	0.627
Basal DAS28-CRP	0.61	0.28	1.35	0.223
Basal CDAI	1.06	0.97	1.15	0.191
Basal ESR	0.99	0.97	1.01	0.393
Basal VAS global	1.01	0.98	1.03	0.594
Infliximab	0.00	0.00		0.980
Etanercept	1.22	0.50	2.93	0.663
Golimumab	1.74	0.36	8.43	0.490
Sertolizumab	0.86	0.11	6.86	0.887
Adalimumab	0.88	0.24	3.25	0.853
Final model				
Median disease duration (years)	0.95	0.90	1.00	0.048

TNF: Tumor necrosis factor, HR: Hazard ratio, CI: Confidence interval, RF: Rheumatoid factor, HAQ: Health Assessment Questionnaire, DAS 28: Disease activity score 28, CRP: C-reactive protein, CDAI: Clinical Disease Activity Index, ESR: Erythrocyte sedimentation rate, VAS: Visual Analog Scale

DISCUSSION

This study, conducted in the TURKBIO registry, suggests that comorbidity in bio-naive patients with RA starting the first TNFi treatment is not associated with a decreased treatment response and shortened retention rate. It is notable that previously identified factors, including gender, age, RF positivity, basal disease activity scores, and smoking, also did not appear to have a significant impact on drug survival for the first TNFi in our cohort.

In most studies presenting real-life data, approximately 50% of patients discontinued biologic therapy or had to switch to an alternative agent within five years after the first bDMARD.[12] The persistence of TNFi treatment in RA patients depends on its effectiveness and tolerability. Prolonged drug survival may indirectly indicate longer remission in RA patients, making it crucial to analyze the contributing factors. Comorbidities play a significant role in affecting the quality of life in RA patients[13] and can potentially limit treatment options. Comorbidities may lead to a preference for less intensive treatment than is indicated. For instance, a study demonstrated that the likelihood of bDMARD usage decreased by 11% with each additional chronic disease.[14] Patients with more than two comorbidities also experienced a longer median time to first biologic agent prescription than those without multimorbidities.[15] This study did not identify a significant relationship between multi-comorbidity and TNFi persistence.

According to the UK cohort, comorbidities such as respiratory and cardiovascular diseases are significantly prevalent in newly diagnosed RA patients.[16] Additionally, RA patients had higher 3-year comorbidity incidence than controls.[17] The European League Against Rheumatism has emphasized the importance of screening for comorbid conditions like infection, accelerated atherosclerosis, osteoporosis, gastrointestinal disorders, malignancies, and depression in RA patients.[18] Additionally, according to the EULAR working group, comorbidities in difficult-to-treat RA may affect the assessment of inflammatory activity.[19] Considering the potential for obesity, infections, malignancies, and fibromyalgia to cause an overestimation of inflammatory markers and/or disease activity, it is crucial to consider these factors in the assessments.[20] In the CORRONA registry, RA patients with more comorbidities are less likely to respond to therapy.[21] However, the UK inception cohort data indicated no correlation between baseline comorbidities and DAS28 outcome at 5 and 10 years.[22] Furthermore, the survival rate with first-line bDMARD was similar for those with and without comorbidities in the Spanish cohort.[23] Similarly, the results of our study suggested that there was no impact of comorbidities on the initial TNFi drug survival or treatment response rates.

Continuation rates of TNFi treatment indirectly show us the effectiveness and safety of the drug. In a study evaluating the real-life 10-year survival of the first TNFi drugs for inflammatory arthritis, 28% discontinued treatment due to ineffectiveness and 24.8% due to side effects.[24] British Society for Rheumatology Biologics Register revealed that 50% of patients discontinued their initial TNFi treatment during a median follow-up of 2 years.[25] Combining with a csDMARD improves bDMARD survival,[25,26] but the RF is negatively associated with biological drug survival.[27] In a multicenter study, higher baseline disease activity and female gender were associated with early TNFi discontinuation.[28] In the Israeli population, the prolonged duration of the first bDMARD medication is associated with male gender, concurrent csDMARD use, and the initiation of bDMARD treatment in earlier calendar years.[29] The use of oral steroids in combination with TNFi treatment has been shown to increase the risk of discontinuation in the ANSWER cohort.[30] In our study, we found that age, gender, baseline activity scores, or RF positivity did not affect the first-line TNFi retention rate.

Limitations

It's important to highlight that this study has some limitations that should be considered. Firstly, the reasons for treatment discontinuation, whether due to lack of efficacy or adverse events, were not explicitly stated. Another limitation is that we did not use a standard comorbidity index such as CCI. Dose calculation for concomitant csDMARD and steroid was not undertaken. Furthermore, we could not differentiate between the effects of the original and biosimilar TNFi.

CONCLUSION

The comorbidities in RA raise essential considerations regarding the impact on disease activity, functional status, and treatment response. However, our study suggests that comorbidities may not be associated with the decreased first TNFi treatment response and lower retention rate. Notably,

previously identified factors such as gender, seropositivity, disease activity scores, and structural damage presence did not significantly impact drug survival for the first TNFi in our cohort. However, it is essential to acknowledge the need for further prospective research to understand how multimorbidity affects disease outcomes and treatment survival comprehensively.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dokuz Eylül University Faculty of Medicine Ethics Committee (Date: 07.06.2013, Decision No: 107354).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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